# This Page Is Inserted by IFW Operations and is not a part of the Official Record

# **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

# IMAGES ARE BEST AVAILABLE COPY.

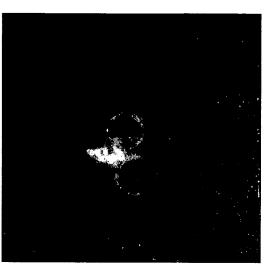
As rescanning documents will not correct images, please do not report the images to the Image Problem Mailbox.

Sheet 1 of 61

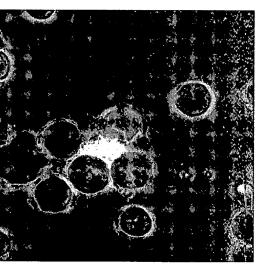
Docket No.: BSZ-050

Figure 1

Fusion of Cochleate Membrane with Target Cells



Fluorescent Image



Phase/Fluorescent Image

Sheet 2 of 61

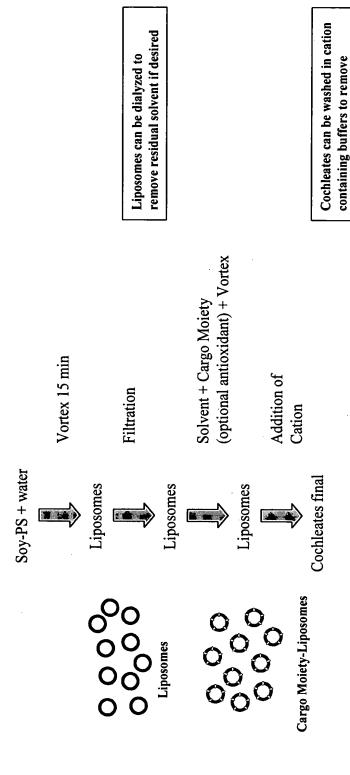
residual solvent if desired

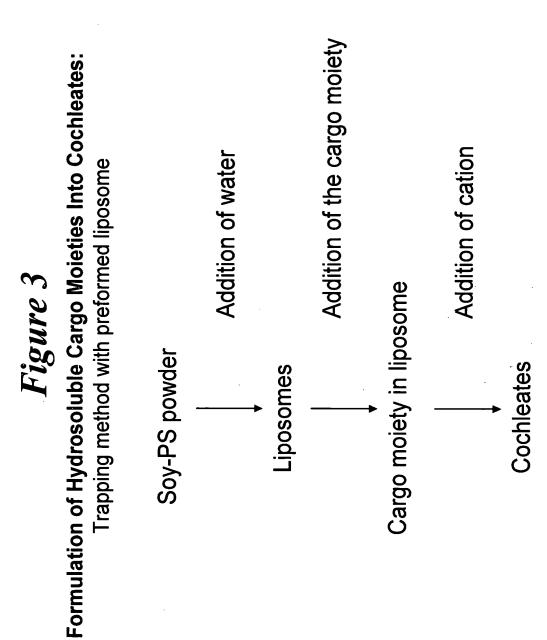
Cargo moiety-Cochleates

Docket No.: BSZ-050

### 2/61

# Formulation of Hydrophobic Cargo Moiety Into Cochleates: Solvent Drip Method

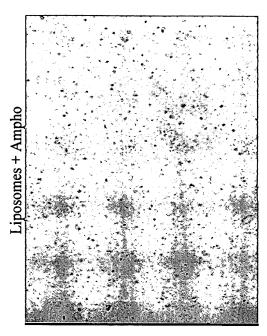




Docket No.: BSZ-050

Sheet 4 of 61

4/61



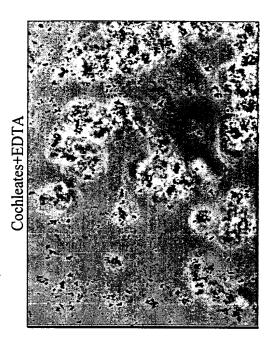
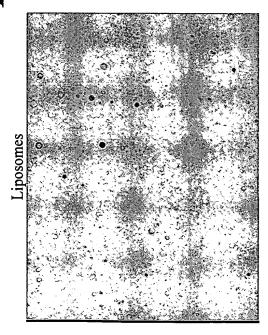
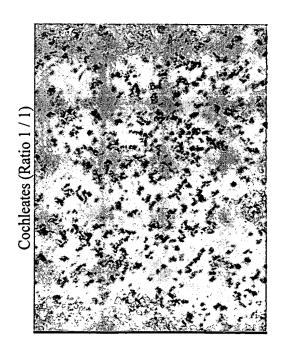


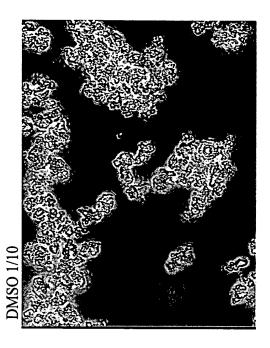
Figure 4

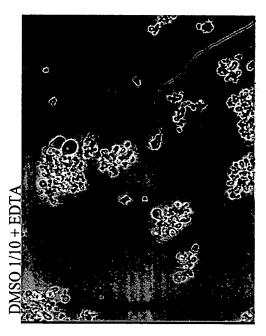




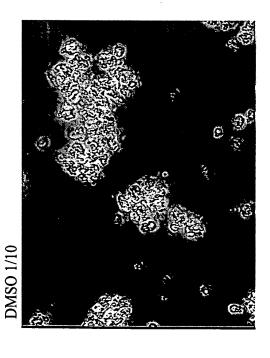
Sheet 5 of 61

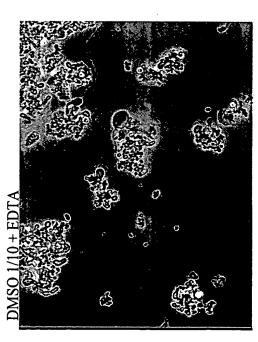
Docket No.: BSZ-050







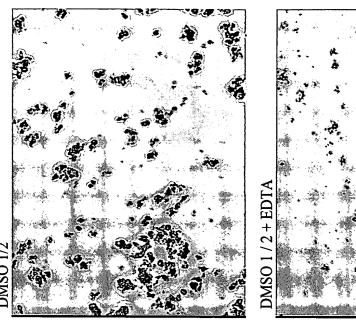


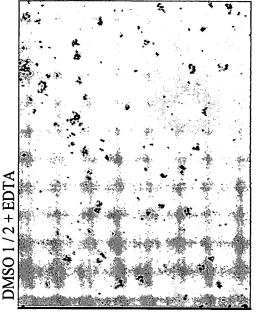


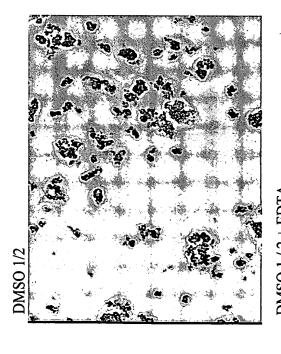
Sheet 6 of 61

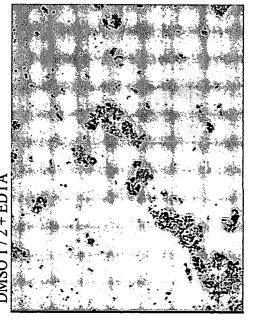
Docket No.: BSZ-050

6/61









Sheet 7 of 61

Docket No.: BSZ-050

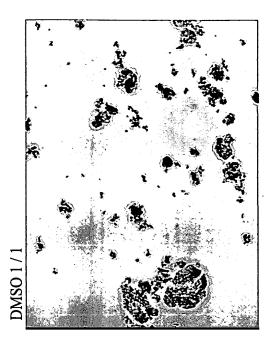
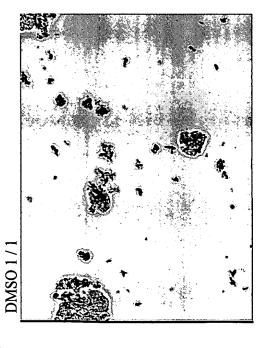
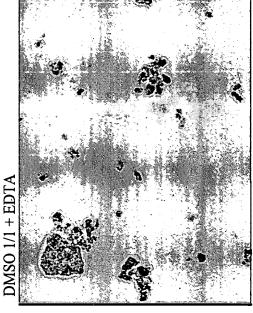


Figure 7





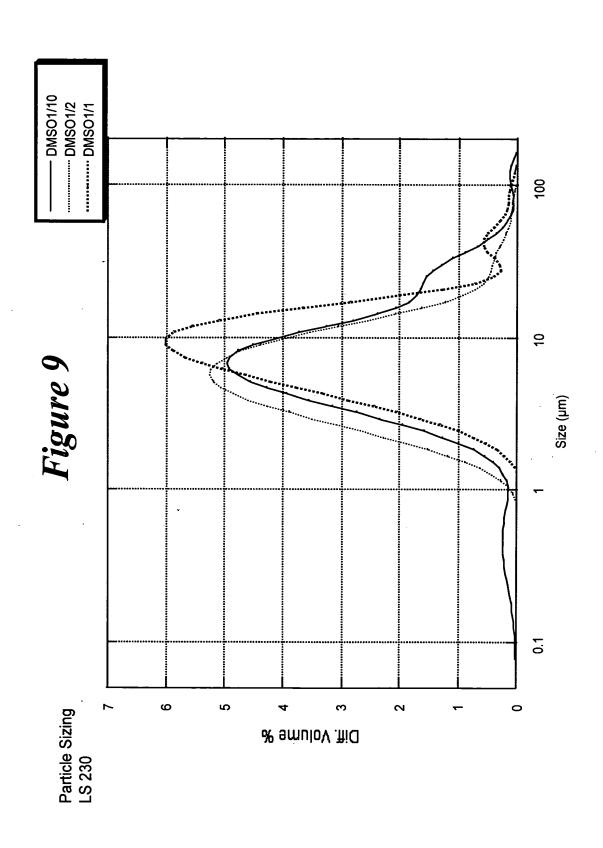
AND METHODS OF USE Sheet 8 of 61 8/61 4 01 1000 Figure 8 100 9 2 0 30 25 20 15 9 ئ ک (%) InuomA

App No.: Not Yet Assigned Docket No.: BSZ-0 Inventor: Raphael J. MANNINO et al.

Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

Sheet 9 of 61

9/61

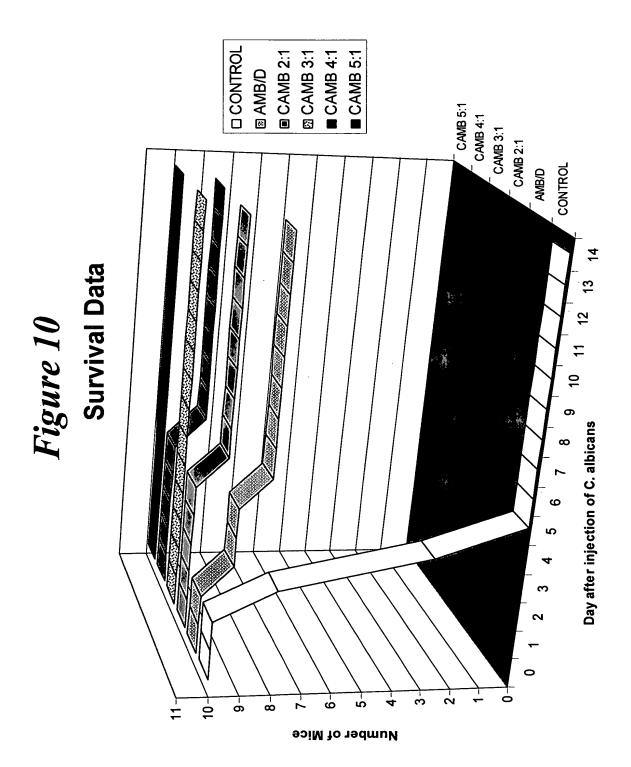


App No.: Not Yet Assigned

Inventor: Raphael J. MANNINO et al.
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES
AND METHODS OF USE

Sheet 10 of 61

Docket No.: BSZ-050



Sheet 11 of 61

11/61

sbunl ⊞ Liver **CAMB 5:1** CAMB 4:1 Comparison of Bacterial Burden for in vivo Study of AmB formulations **CAMB 3:1** 3500 3000 2500 2000 9 0 50 20 average (CFU/gram of tissue) 300

Figure 1.

App No.: Not Yet Assigned Inventor: Raphael J. MANNINO et al.

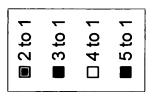
Inventor: Raphael J. MANNINO et al.
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE

Figure 12

Sheet 12 of 61

12/61



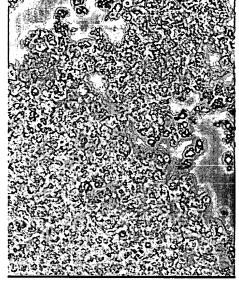
Amphotericin B Efficacy In Vitro in Macrophages 0.001ug W Concentration (ug/ml) 0.01ug 0.1ug 250-200-150-50-100 CFU's

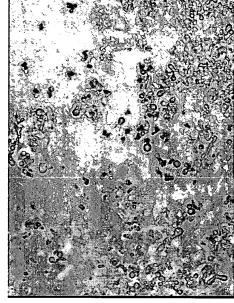
AND METHODS OF USE

Sheet 13 of 61

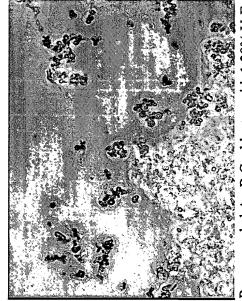
Docket No.: BSZ-050

13/61





Re-suspended AmB Cochleates with 1.28% V-E (AmB to V-E W/W)



Re-suspended AmB Cochleates with 1.28% V-E (AmB to V-E w/w) and After Adding EDTA

AND METHODS OF USE

Sheet 14 of 61

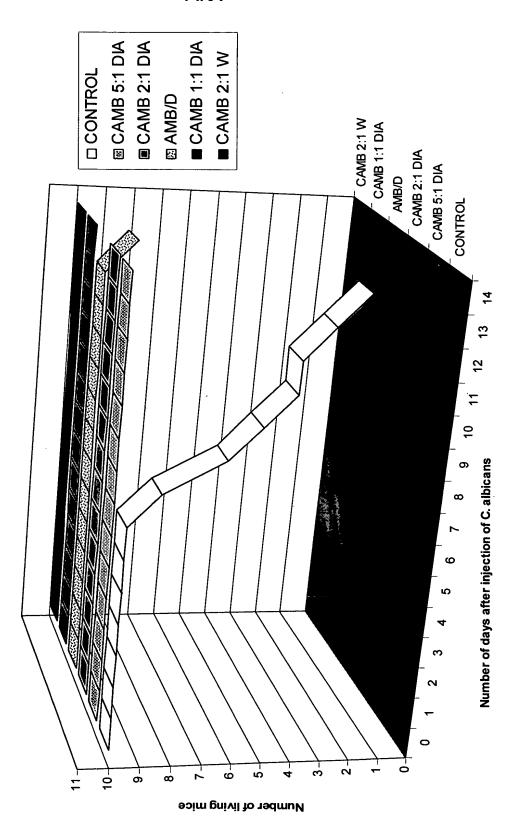


Figure 14 SURVIVAL DATA

AND METHODS OF USE

Sheet 15 of 61

15/61

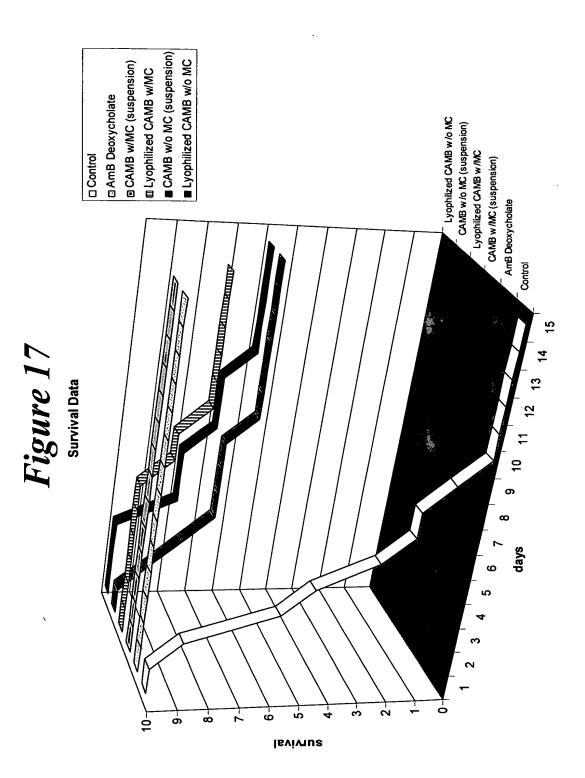
🔳 ungs CAMB 2:1 WASH (2mg/kg) CAMB 1:1 DIA (2mg/kg) Companison of Bacterial Burden for in vivo Study of AmB formulations CAMB 5:1 DIA (2mg/kg) CAMB 2:1 DIA (2mg/kg) · AMB/D (2mg/kg) 2000 1800 1600 1400 1200 800 200 400 average (CFU/gram of tissue) X 100

Figure 15

App No.: Not Yet Assigned Docket No.: BSZ-0 Inventor: Raphael J. MANNINO et al.
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES AND METHODS OF USE Docket No.: BSZ-050 Sheet 16 of 61 16/61 ☑ Dialysis 2/1 Dialysis 5/1 ■ Dialysis 1/1 ☑ Wash 2/1 ■ AMB/D 0.001 In Vitro Efficacy of AmB Cochleates Figure 16 Concentration (ug/ml) 0.01 9. 2000 1500 200 1000 CEn.2

Sheet 17 of 61

17/61



App No.: Not Yet Assigned Inventor: Raphael J. MANNINO et al.

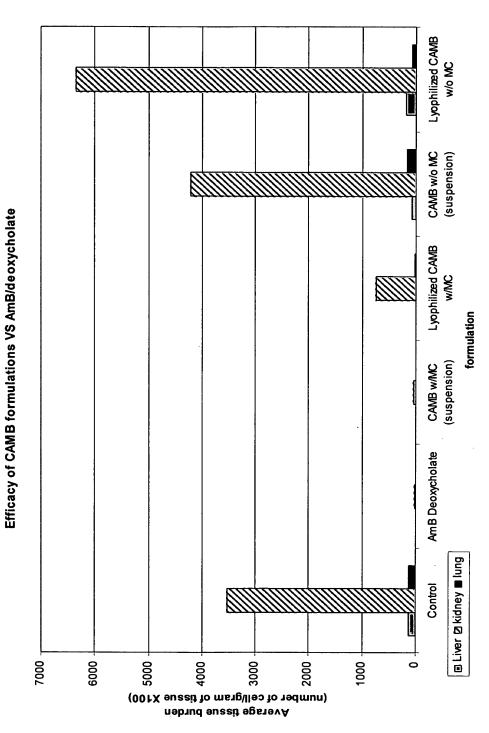
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE

Sheet 18 of 61

Docket No.: BSZ-050

18/61



Sheet 19 of 61 19/61 tyrphostin cochleates x free tyrphostin 口 8000 Kinetics of Tyrphostin in Cochleates vs. Free Figure 19 0009 X × 2000 × 0 1 10 <sup>6</sup> , 8 10 <sup>5</sup> ) 2 10 5 2 ß 0 6 10 Peak Area

App No.: Not Yet Assigned Inventor: Raphael J. MANNINO et al.

AND METHODS OF USE

Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE Sheet 20 of 61 20/61 Kinetics of Impurity 1 in Cochleates vs. Free 1 104 8000 9009 4000 口 × 믑 free impurity2 cochleates impurity2 2000 ×× 믑 × 0 Figure 20 -2000 ΧД 6 10<sup>5</sup> 3 10<sup>5</sup> 1 105 5 10<sup>5</sup> 4 10<sup>5</sup> 0 2.10<sup>5</sup> **besk** агеа Kinetics of Impurity 2 in Cochleates vs. Free x free impurity1
☐ Cochleates impurity1 8000 0009 口 4000 × 日 ×× 믭 0 2 10<sup>5</sup> 1 10° 8 10<sup>5</sup> 6 10<sup>5</sup> 4 10<sup>5</sup> **besk** вгев

App No.: Not Yet Assigned Docket No.: BSZ-0 Inventor: Raphael J. MANNINO et al.

Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

App No.: Not Yet Assigned Inventor: Raphael J. MANNINO et al.

Inventor: Raphael J. MANNINO et al.

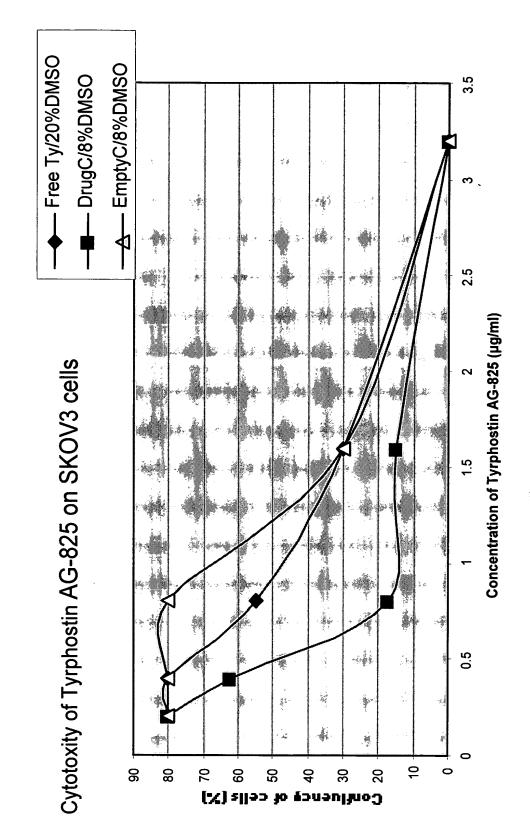
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE

Figure 21

Sheet 21 of 61

21/61

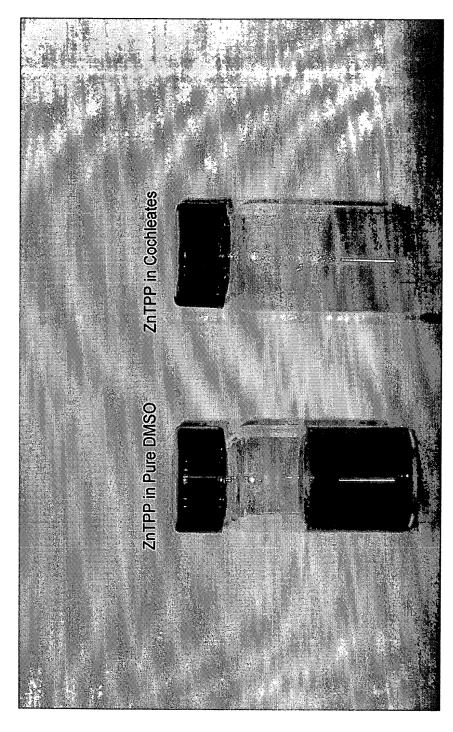


Sheet 22 of 61

Docket No.: BSZ-050

22/61





AND METHODS OF USE

Sheet 23 of 61

Fluorescence

Addition of EDTA

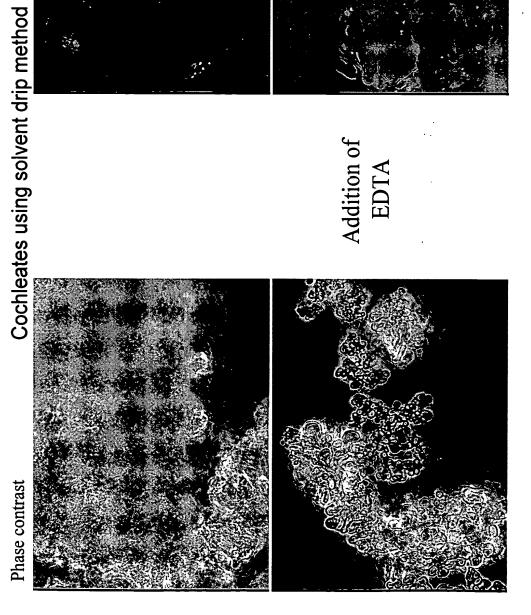
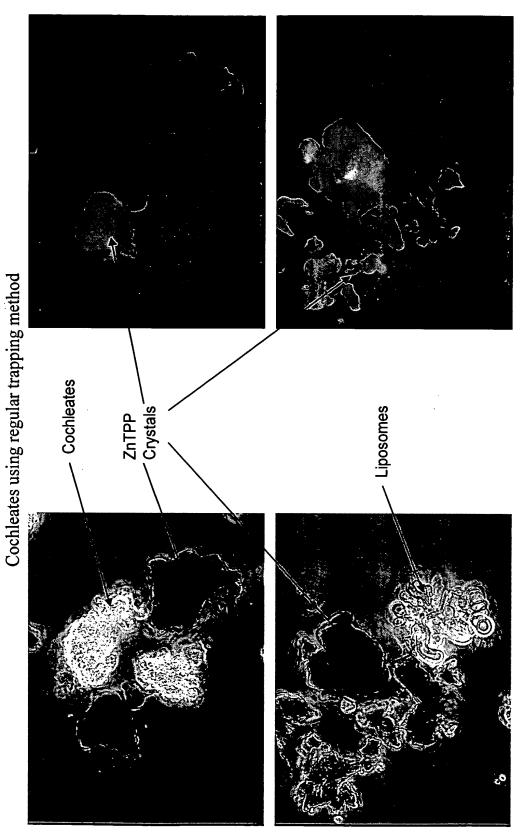


Figure 23

Sheet 24 of 61

Docket No.: BSZ-050

24/61



Sheet 25 of 61

Docket No.: BSZ-050

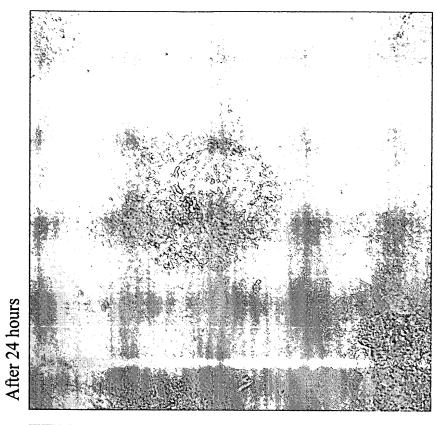
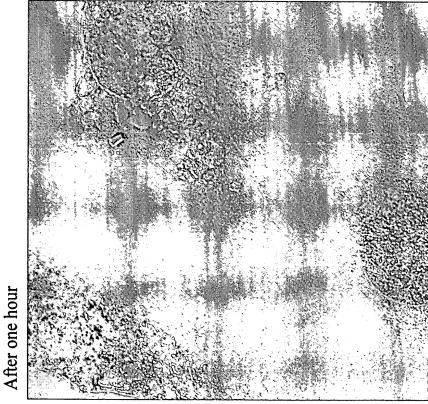


Figure 25



ZnTPP in cochleates

Sheet 26 of 61

Docket No.: BSZ-050

# 26/61

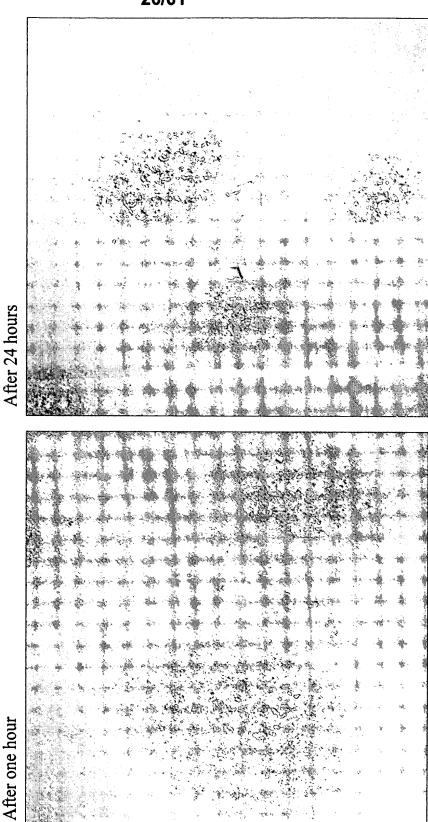


Figure 26

ZnTPP in solution in DMSO

Sheet 27 of 61

Docket No.: BSZ-050

27/61

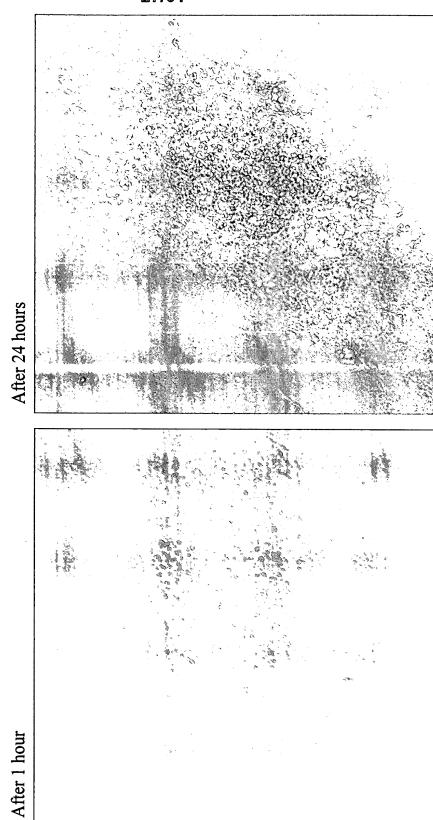


Figure 27

Cochleates containing Pyrene DOPE

App No.: Not Yet Assigned

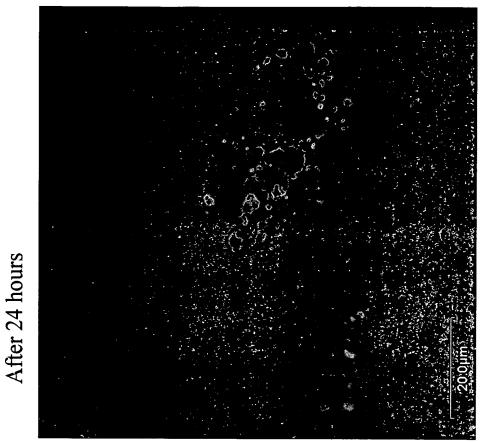
Inventor: Raphael J. MANNINO et al.
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE

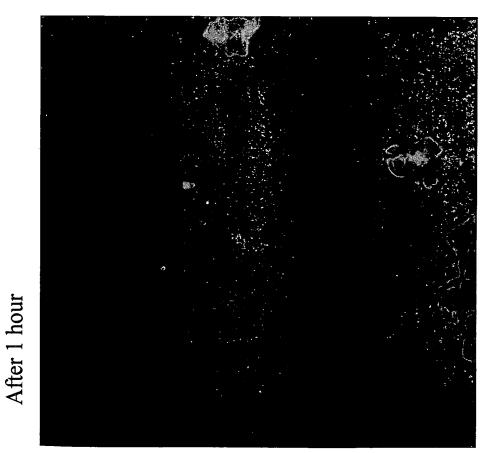
Sheet 28 of 61

Docket No.: BSZ-050

28/61



 $Figure \ 28$  Cochleates containing Pyrene DOPE and ZnTPP



App No.: Not Yet Assigned Docket No.: BSZ-0 Inventor: Raphael J. MANNINO et al.
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES AND METHODS OF USE Docket No.: BSZ-050 Sheet 29 of 61 29/61 + Calcium Porphyrin Cochleates Phase 1000x Porphyrin Liposomes Cochleates Fluorescence 1000x Phase 1000x + EDTA + EDTA Figure 29 Liposomes Liposomes + Buffer Porphyrin in DMSO Soy-PS Powder

App No.: Not Yet Assigned Docket No.: BSZ-0 Inventor: Raphael J. MANNINO et al.
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES AND METHODS OF USE Docket No.: BSZ-050 Sheet 30 of 61 30/61 Aggregation Inhibitors Aqueous Buffer 0

App No.: Not Yet Assigned Inventor: Raphael J. MANNINO et al.

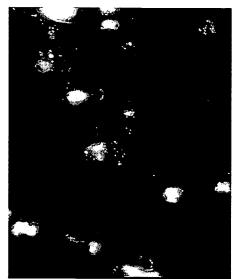
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE

Sheet 31 of 61

Docket No.: BSZ-050

### 31/61



*In vitro* uptake of Rho-PE-lipid precipitates Figure 33A



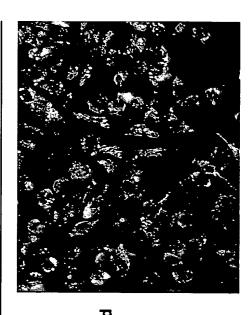
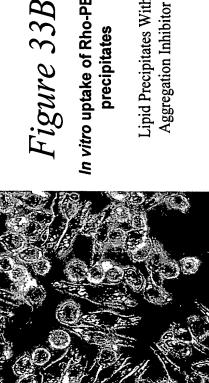


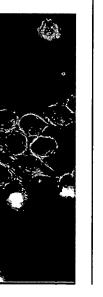
Figure 33B



In vitro uptake of Rho-PE-lipid Lipid Precipitates With precipitates



Fluorescence



App No.: Not Yet Assigned Docket No.: BSZ-050 Inventor: Raphael J. MANNINO et al.

Inventor: Raphael J. MANNINO et al.

Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE

Sheet 32 of 61

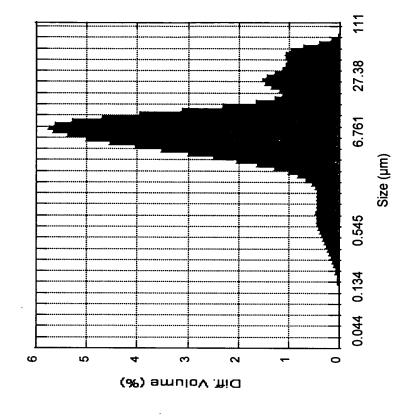
32/61

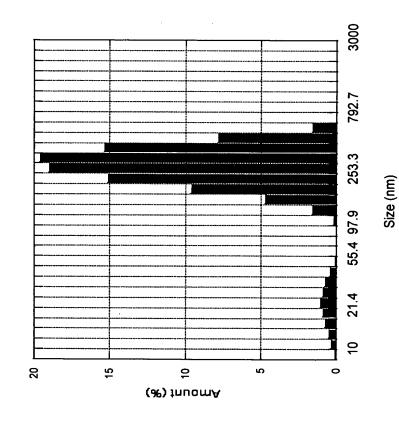
Figure 34B

Lipid Precipitates Without Aggregation Inhibitor

Lipid Precipitates With Aggregation Inhibitor

Figure 34A

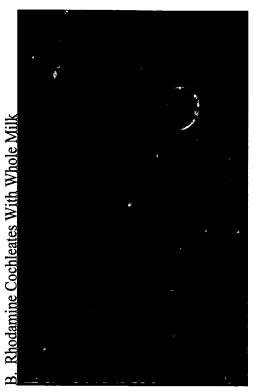


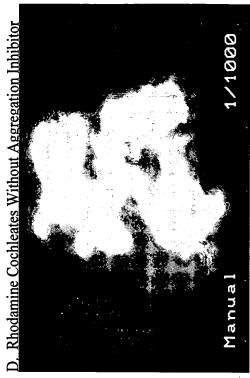


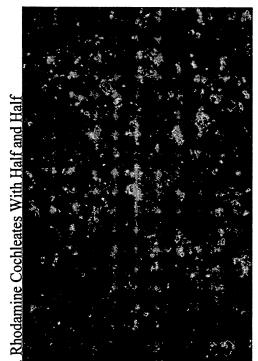
AND METHODS OF USE

Sheet 33 of 61

Docket No.: BSZ-050







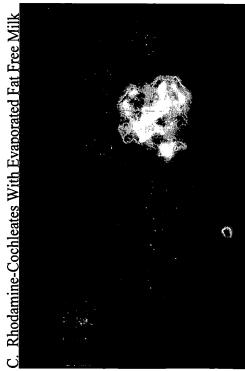


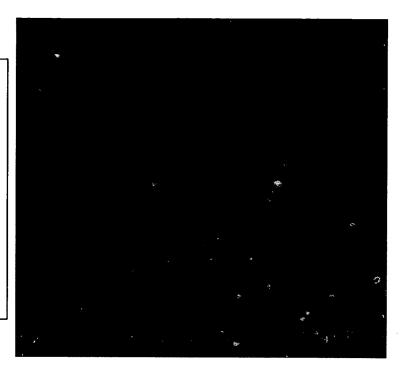
Figure 35

Sheet 34 of 61

Docket No.: BSZ-050

34/61

B: Rhodamine Cochleates With Milk



A: Rhodamine Cochleates Prior to Addition of Milk

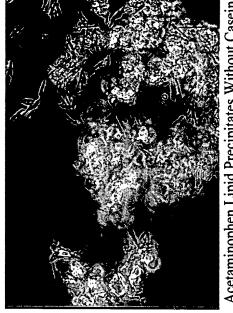


AND METHODS OF USE

Sheet 35 of 61

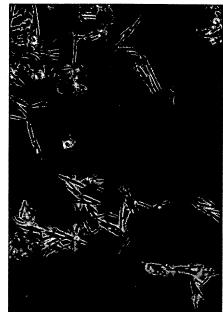
Docket No.: BSZ-050

35/61



Acetaminophen Lipid Precipitates Without Casein

Figure 37B



Aspirin Lipid Precipitates Without Casein

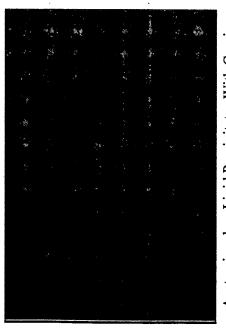
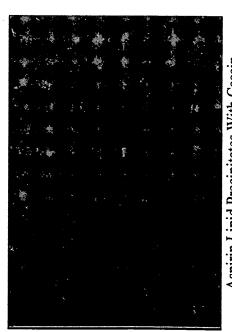


Figure 37A

Acetaminophen Lipid Precipitates With Casein

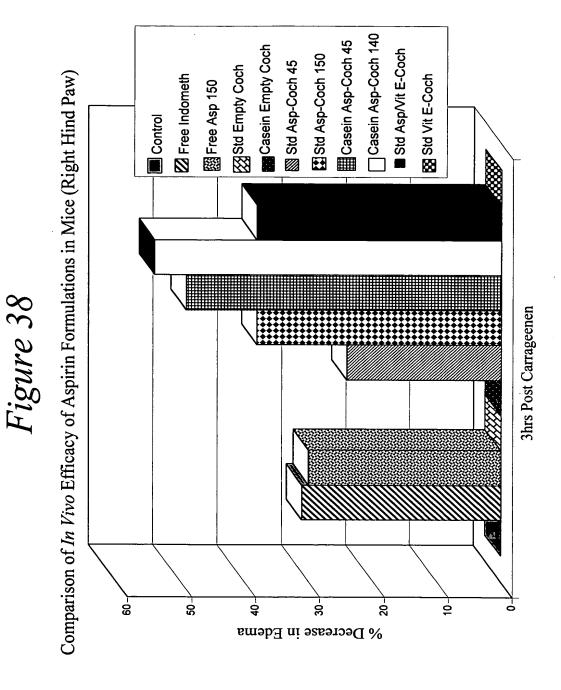


Aspirin Lipid Precipitates With Casein

App No.: Not Yet Assigned Docket No.: BSZ-Conventor: Raphael J. MANNINO et al.
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE

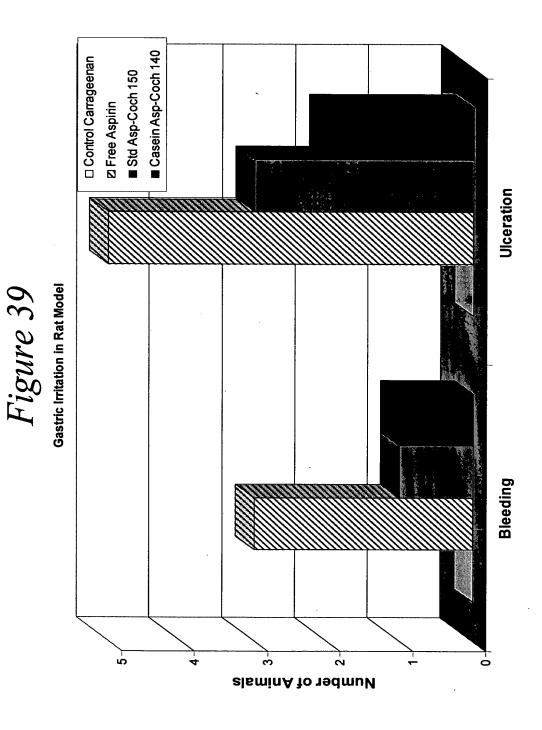
Sheet 36 of 61



AND METHODS OF USE

Sheet 37 of 61

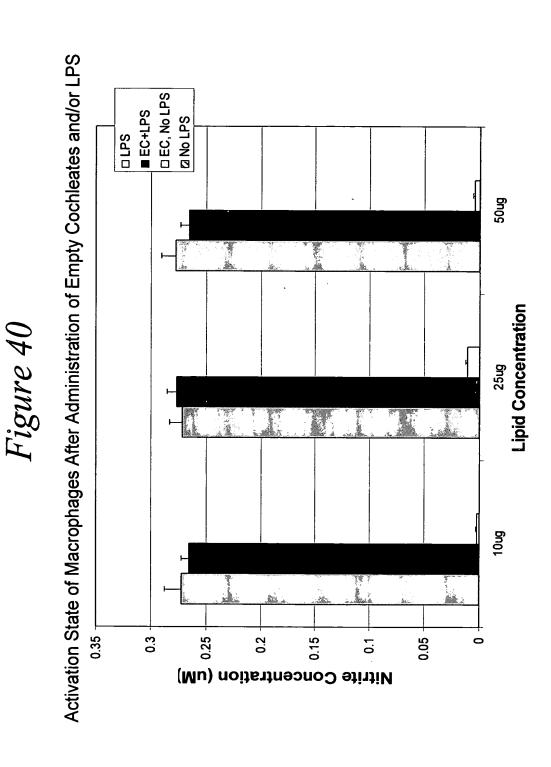
Docket No.: BSZ-050



Docket No.: BSZ-050

Sheet 38 of 61

38/61



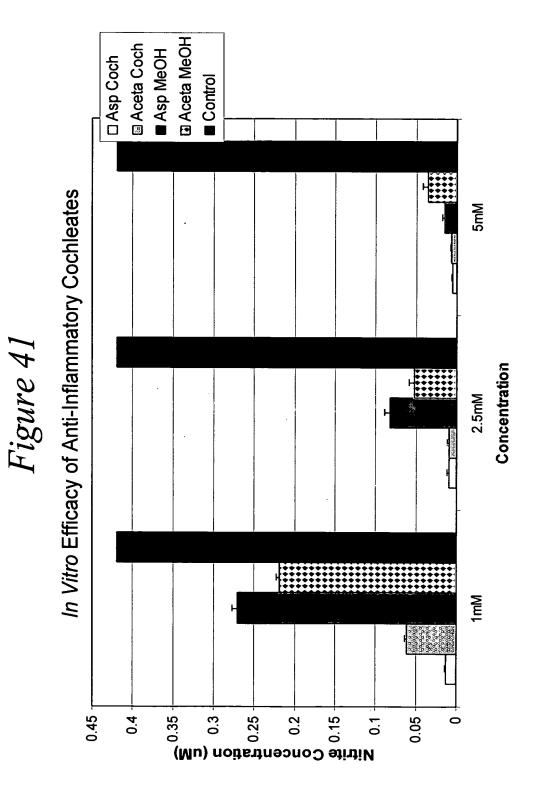
App No.: Not Yet Assigned

Inventor: Raphael J. MANNINO et al.
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE

Sheet 39 of 61

39/61



AND METHODS OF USE

Sheet 40 of 61

## 40/61

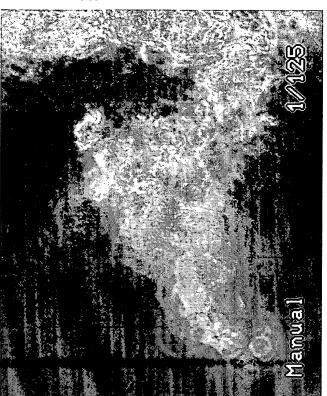
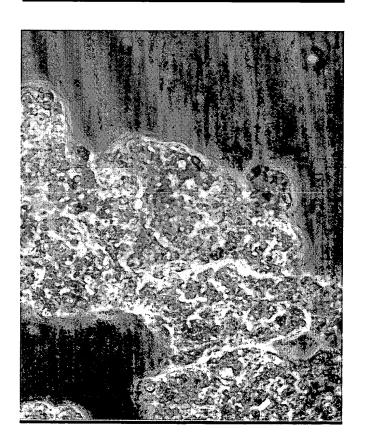


Figure 42

Figure 43



Sheet 41 of 61

Docket No.: BSZ-050

41/61

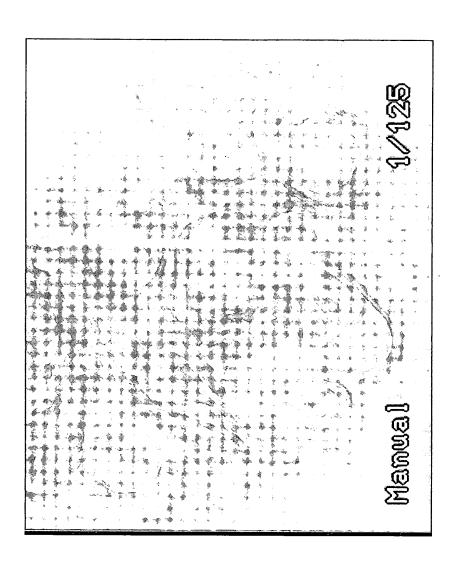
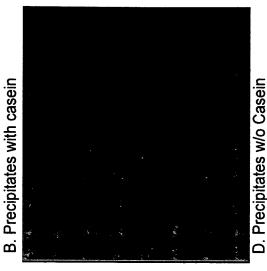


Figure 44

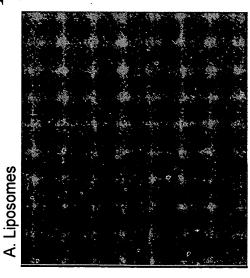
Docket No.: BSZ-050

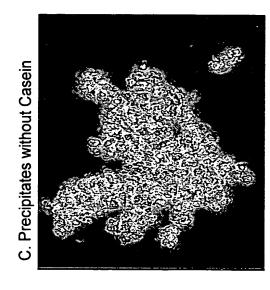
Sheet 42 of 61



upon addition of EDTA

Figure 45





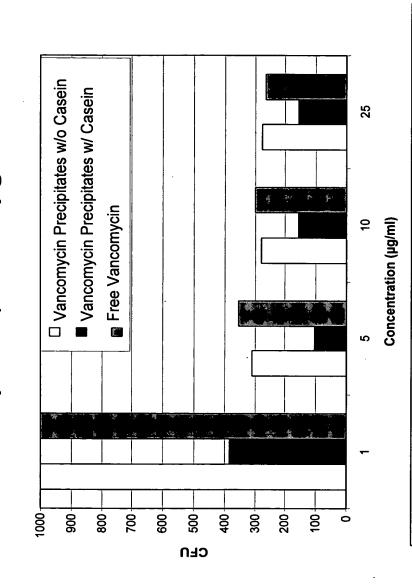
App No.: Not Yet Assigned Docket No.: BSZ-0 Inventor: Raphael J. MANNINO et al.
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES AND METHODS OF USE

Sheet 43 of 61

43/61

Vancomycin Precipitate Efficacy @ 3hrs

Figure 46



In Vitro Efficacy of Vancomycin Precipitates in Macrophages Infected with Staphylococcal aureus at 3 hours post infection.

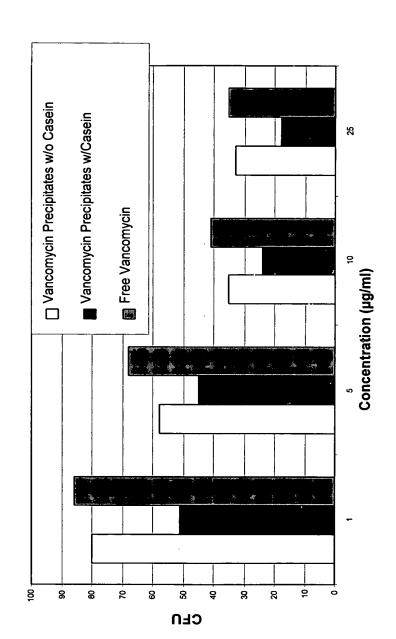
App No.: Not Yet Assigned Docket No.: BSZ-0 Inventor: Raphael J. MANNINO et al.
Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES AND METHODS OF USE

Sheet 44 of 61

44/61

Vancomycin Precipitates Efficacy @ 6hrs

Figure 47



In Vitro Efficacy of Vancomycin Precipitates in Macrophages Infected with Staphylococcal aureus at 6 hours post infection.

App No.: Not Yet Assigned Docket No.: BSZ-0 Inventor: Raphael J. MANNINO et al.

Title: NOVEL ENCOCHEATION METHODS, COCHLEATES

AND METHODS OF USE

Sheet 45 of 61

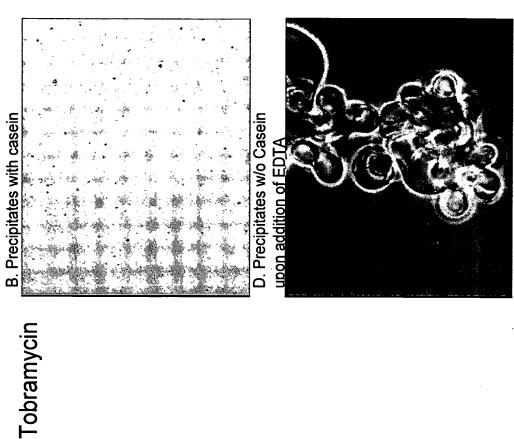
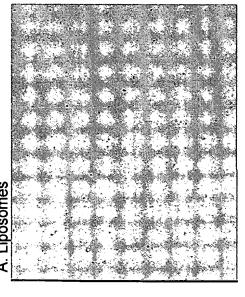
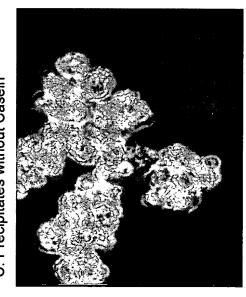


Figure 48





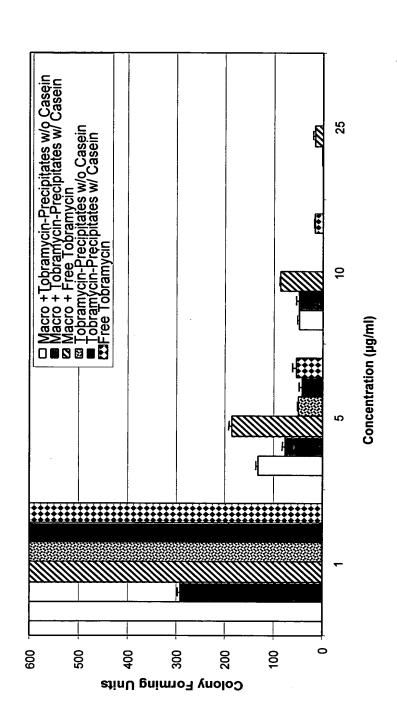


AND METHODS OF USE

Sheet 46 of 61

Docket No.: BSZ-050

Pseudomonas aeruginosa at 3 Hours Post-Infection **Efficacy of Tobramycin Formulations Against** 

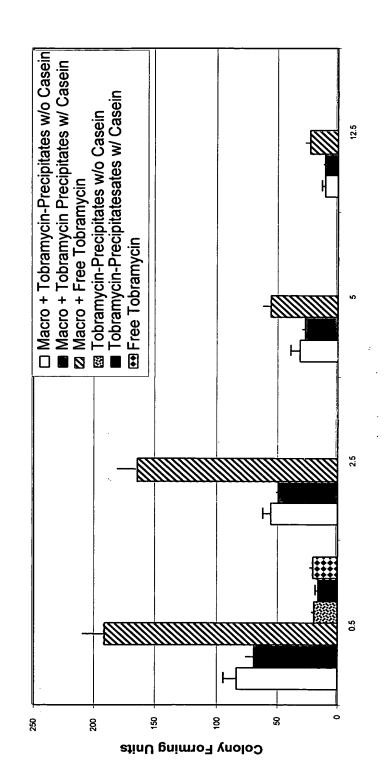


AND METHODS OF USE

Sheet 47 of 61

47/61

Pseudomonas aeruginosa at 6 Hours Post-Infection **Efficacy of Tobramycin Formulations Against** 



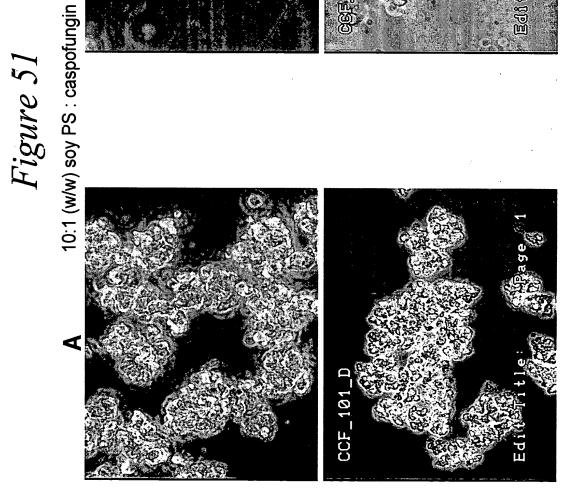
Concentration (µg/ml)

AND METHODS OF USE

Sheet 48 of 61

Docket No.: BSZ-050

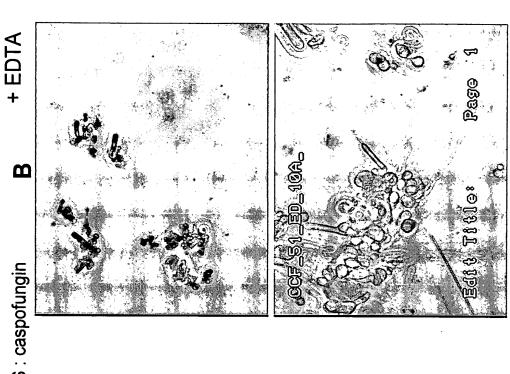
 $\mathbf{\omega}$ 



AND METHODS OF USE

Sheet 49 of 61

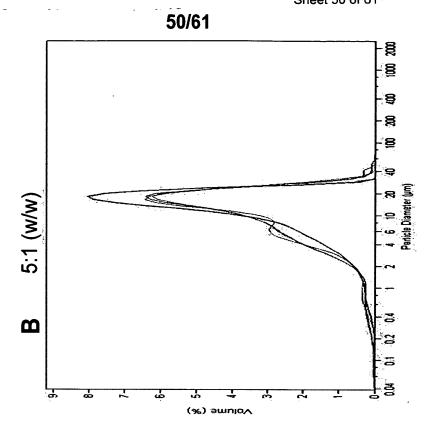
49/61

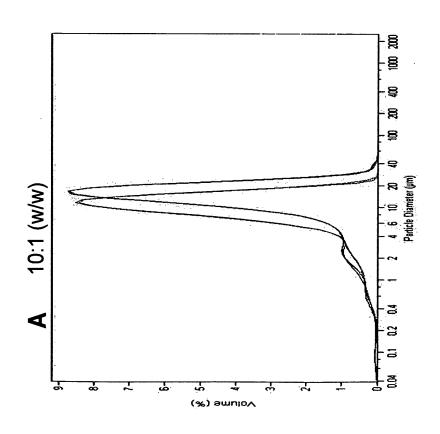


5:1 (w/w) soy PS: caspofungin

AND METHODS OF USE

Sheet 50 of 61



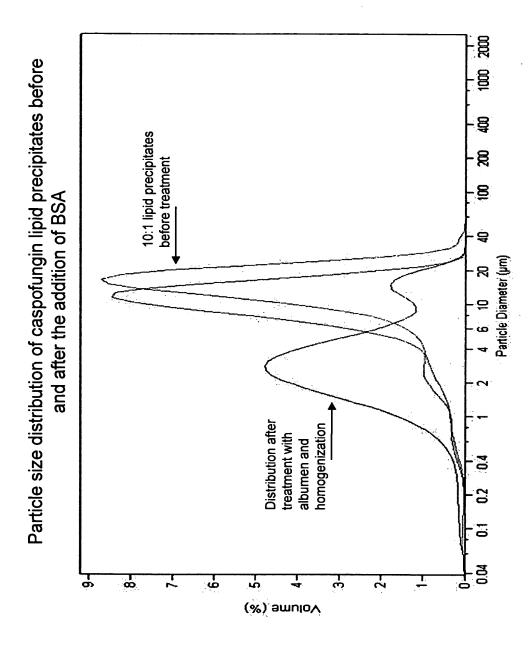


Docket No.: BSZ-050

Figure 54

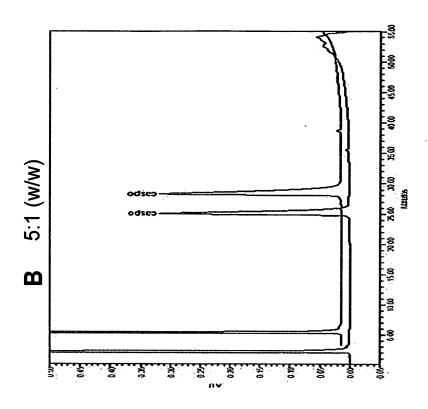
Sheet 51 of 61

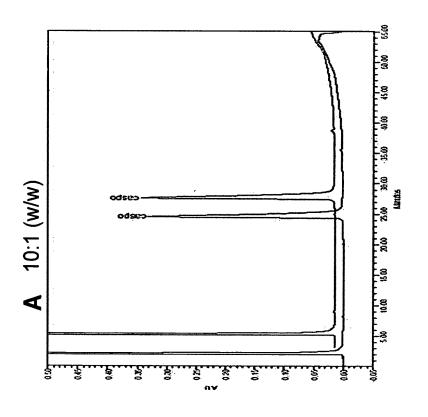
51/61



Sheet 52 of 61

52/61





Sheet 53 of 61

Docket No.: BSZ-050

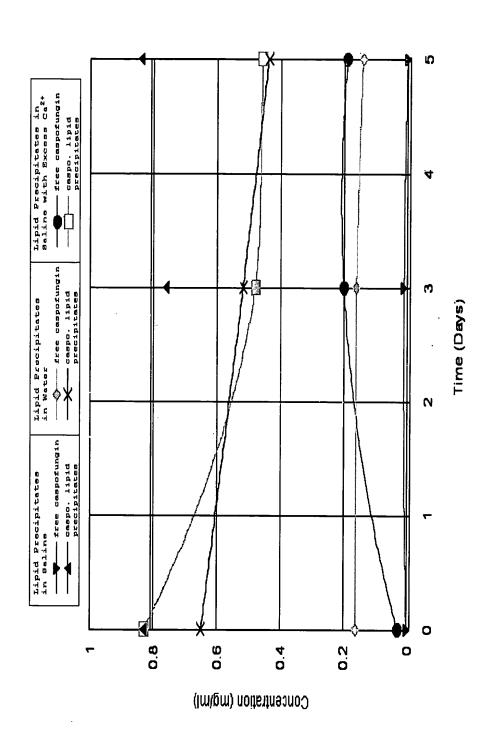


Figure 56

App No.: Not Yet Assigned Docket No.: BSZ-0 Inventor: Raphael J. MANNINO et al.

Title: NOVEL ENCOCHEATION METHODS, COCHLEATES Docket No.: BSZ-050 AND METHODS OF USE Sheet 54 of 61 54/61 9=Hd 6=Hd 2=Hd 9=Hd

pH=4

Structure of caspofungin lipid precipitates as a function of pH.

Figure 57

App No.: Not Yet Assigned Inventor: Raphael J. MANNINO et al.

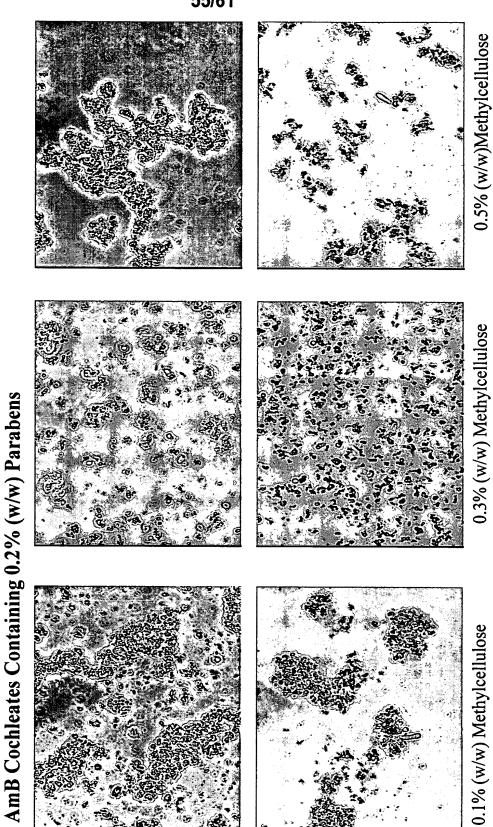
Inventor: Raphael J. MANNINO *et al.*Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE

Figure 58

Sheet 55 of 61

Docket No.: BSZ-050



App No.: Not Yet Assigned Inventor: Raphael J. MANNINO et al.

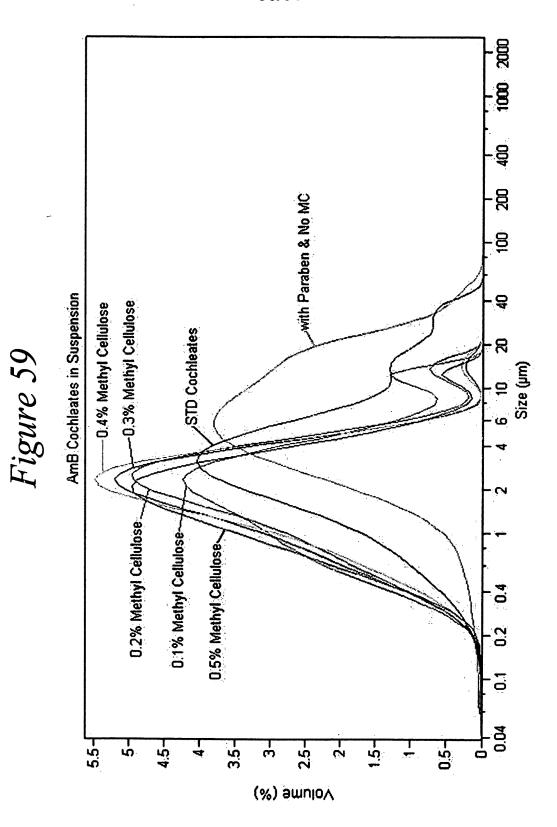
Inventor: Raphael J. MANNINO et al.

Title: NOVEL ENCOCHLEATION METHODS, COCHLEATES

AND METHODS OF USE

Sheet 56 of 61

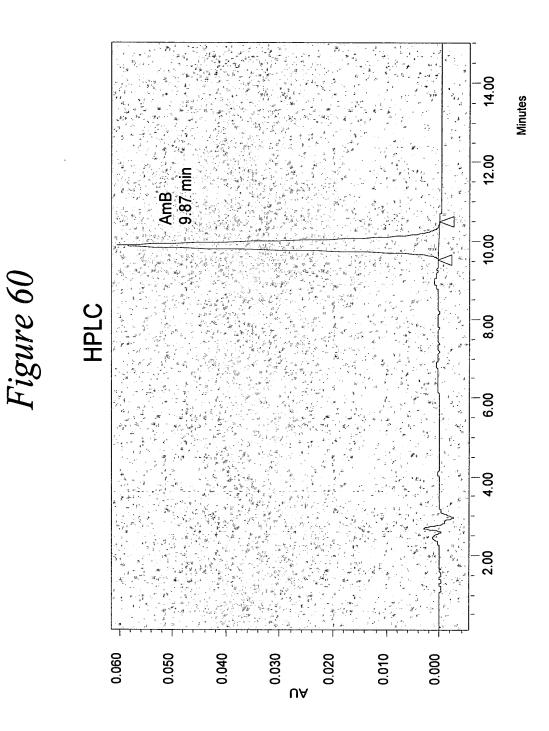
56/61



AND METHODS OF USE

Sheet 57 of 61

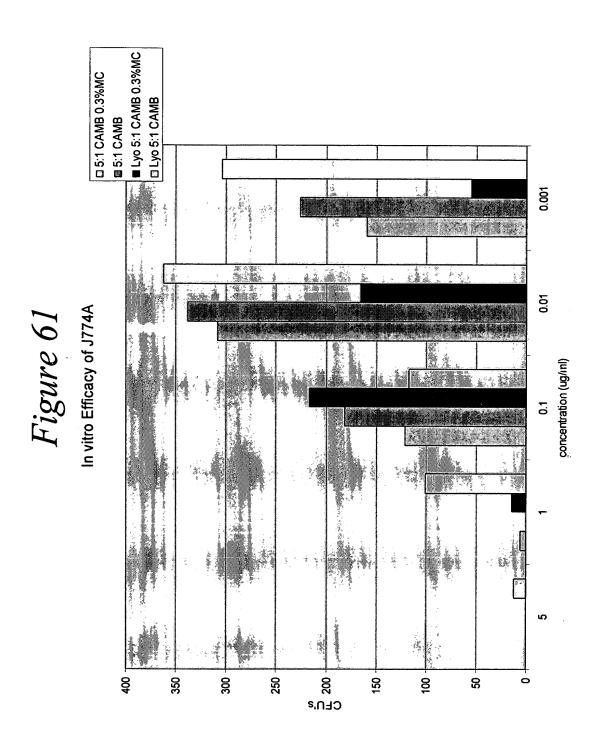
57/61



Docket No.: BSZ-050

AND METHODS OF USE

Sheet 58 of 61



AND METHODS OF USE

Sheet 59 of 61

59/61

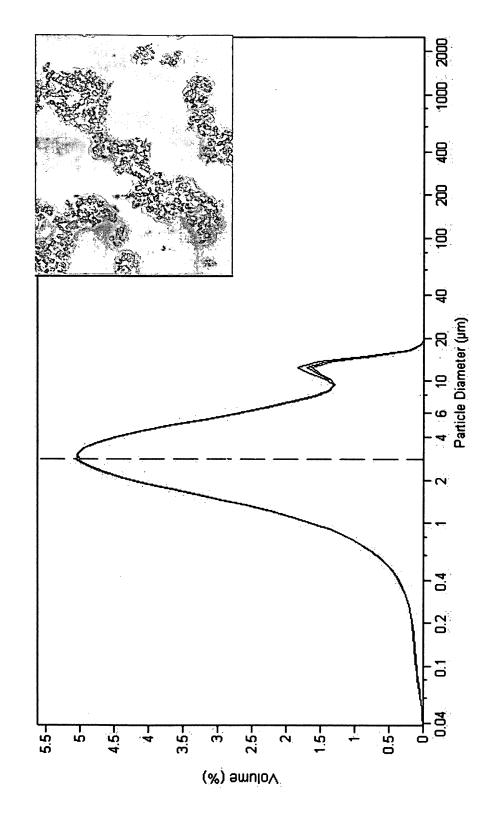


Figure 62

AND METHODS OF USE

Sheet 60 of 61

Docket No.: BSZ-050

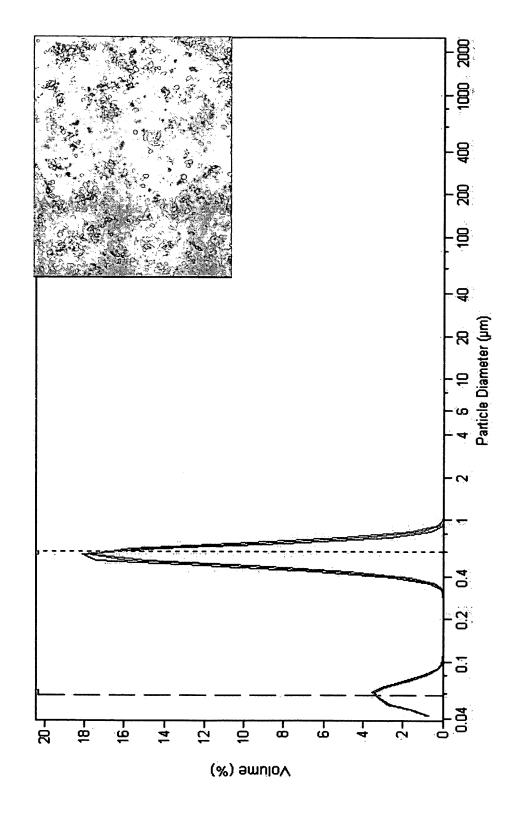


Figure 63

Docket No.: BSZ-050

AND METHODS OF USE

Sheet 61 of 61

